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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/147,693	02/17/99	LUBITZ W	P564-9005

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EXAMINER	
SANDALS, W	
ART UNIT	**PAPER NUMBER**
1636	4
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/147,693	Applicant(s) Lubitz et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Feb 17, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-37* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *14* is/are allowed.

☒ Claim(s) *1-13 and 15-37* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Drawings

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

3. A sequence appears at page 19 of the Specification which is not identified by a sequence identifier. Correction is required.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned.

Claim Objections

4. Claims 6-13, 15-30 and 34-37 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 29, 30, 36 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims recited broadly encompass any bacterial live or ghost cell as a vaccine and a method of use.

The specification provides insufficient guidance of how to make and use a bacterial live or ghost cell as a vaccine. It is well recognized in the art that is unclear whether an antigen, in this case a live or ghost bacterial cell, will elicit protective immunity. Ellis, R. W. (see Chapter 29 of "VACCINES" [Plotkin, S. A. et al., (ed.), published by W.B. Saunders Company (Philadelphia) in 1988, see especially page 571, second full paragraph] exemplifies this problem

in the recitation that "[t]he key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies...and thus protect the host against attack by the pathogen".

Since:

1. no working examples are set forth in the specification of the protein useful for vaccination; and

2. the art teaches the unpredictability of using an antigen for vaccination,

it would be an undue burden and be unpredictable for a skilled artisan to make and use a vaccine comprising live or ghost bacterial cells as broadly claimed.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-3, 9-18, 34, 35 and 37 (and all dependent claims) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step is a correlation, or recapitulation step at the end of the claim which restates the preamble.

10. Claims 2 and 3 recite the limitation "recombinant variants". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A recombinant variant of a phage may be closely patterned after the subject phage or may be very loosely patterned after the subject phage, such that it may bear no resemblance or form recognizable as the subject phage which may be chemically and/or biologically totally unrelated in function or form to the subject phage.

11. Claims 9-14, 16 recite the limitation "mutated lambda". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A mutated lambda phage may be closely patterned after the subject phage or may be very loosely patterned after the subject phage, such that it may bear no resemblance or form recognizable as the subject phage which may be chemically and/or biologically totally unrelated in function or form to the subject phage.

12. Claim 13 recite the limitation "variant of the sequences". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A variant of the sequences may be closely patterned after the subject variant of the sequences or may be very loosely patterned after the subject variant of the sequences, such that it may bear no resemblance or form recognizable as the subject variant of the sequences which may be chemically and/or biologically totally unrelated in function or form to the subject variant of the sequences.

13. Claims 15-18 provide for the use of a mutated lambda O_R or O_L , but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process

applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 15-18 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

14. Claims 34 and 35 recite the limitation "mutated operator sequence". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A mutated operator sequence may be closely patterned after the subject mutated operator sequence or may be very loosely patterned after the subject mutated operator sequence, such that it may bear no resemblance or form recognizable as the subject mutated operator sequence which may be chemically and/or biologically totally unrelated in function or form to the subject mutated operator sequence.

15. Claim 37 provides for the use of a vaccine composition , but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 37 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e.,

results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-5, 8-13, 15-19 and 22-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eliason et al. in view of Pakula et al.

The claims are drawn to a method for selecting mutated O_R or O_L operator DNA sequences from lambdiod phages which have different thermostability compared to wild-type sequence with regard to binding a repressor wherein the operator DNA sequence is subjected to mutation and selected for different thermostability from the wild type with respect to binding of a repressor. The repressor may be cI857, and the thermostability may be increased from 3-10° or 7-9°. The claims are also drawn to the mutated O_R or O_L operator DNA sequences from lambdiod phages which may be incorporated into a vector, and to a host bacterial cell.

Eliason et al. taught (see especially the abstract, the introduction, page 2342 and the tables and figures) a method for selecting mutated O_R or O_L operator DNA sequences from

lambdiod phages which have different binding compared to wild-type sequence with regard to binding a repressor wherein the operator DNA sequence is subjected to mutation and selected for different binding from the wild type with respect to binding of a repressor. Eliason et al. also taught mutated O_R or O_L operator DNA sequences from lambdiod phages which may be incorporated into a vector, and to a host bacterial cell.

Eliason et al. did not teach that the repressor may be cI857, and the thermostability may be increased from 3-10° or 7-9°.

Pakula et al. taught (see especially the abstract, introduction and the discussion) the change in thermal stability of a mutated repressor protein with the lambda operator. Pakula et al. discuss in great detail, the importance of the contact bases in the operator, and the manner in which they interact with the amino acids of the repressor protein. From their discussion, it is clear that the increased thermal stability of the binding of the repressor protein is directly related to the thermodynamics of the molecular interaction between the contact bases of the operator DNA sequence and the contact amino acids of the repressor protein. Pakula et al. taught that one of skill in the art would be able to select mutated sequences in the repressor protein which would have greater binding affinity for the operator sequences and therefore higher thermostability.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the mutated DNA lambda operator sequences of Eliason et al. with the increased thermostability of repressor sequences of Pakula et al. since Pakula et al. taught the increased thermostability of the repressor complex was due to changes in the thermodynamic

molecular interaction of specific bases and amino acids in the binding site of the operator/repressor pair. Eliason et al. taught the changes in the operator sequence would affect the thermodynamic stability of the interaction of the operator/repressor complex. Since cI857 is a known repressor mutant of the lambda operator, and mutations of the sequence of the cI857 would also be affected by the same thermodynamic laws which apply to the repressor/operator complexes of Eliason et al. and Pakula et al., it would have also been obvious to practice the invention with cI857.

One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the mutated DNA lambda operator sequences of Eliason et al. with the increased thermostability of operator/repressor binding of Pakula et al. since Pakula et al. taught in the abstract that "two suppressor substitutions increase the thermal stability of Cro by 12° C to 14° C.", and in the introduction, "two substitutions that dramatically increase the thermal stability" of the repressor complex was due to changes in the thermodynamic molecular interaction of specific bases and amino acids in the binding site of the operator/repressor pair (see especially figure 4). Eliason et al. taught in the abstract and in the introduction that the changes in the operator sequence would affect the thermodynamic stability of the interaction of the operator/repressor complex. Since cI857 is a known repressor mutant of the lambda operator, and mutations of the sequence of the cI857 would also be affected by the same thermodynamic laws which apply to the repressor/operator complexes of Eliason et al. and Pakula et al., it would have also been obvious to practice the invention with cI857. Further, a person of ordinary skill in

the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Eliason et al. with Pakula et al.

18. Claims 19-21 and 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eliason et al. in view of Pakula et al. as applied to claims 1-5, 8-13, 15-19 and 22-28 above, and further in view of Vasquez et al.

The claims are drawn to the mutated lambda operator sequence and methods of use as described above, and to a construct where the sequence is in operative linkage with a suicide gene.

Vasquez et al. taught (see especially the abstract, introduction, tables and figures) a lambda operator sequence in operative linkage with a suicide gene.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the lambda operator sequences of Eliason et al. and Pakula et al. which were in operative linkage to an antibiotic resistance gene with the suicide gene taught by Vasquez et al. which was in operative linkage with the lambda operator sequence because Vasquez et al. taught in the abstract that the use of a suicide gene inoperative linkage with the operator gene of the construct allowed the selective expression of a desired gene such as the antibiotic resistance gene of Eliason et al. and Pakula et al.

One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the lambda operator sequences of Eliason et al. and Pakula et al.

which were in operative linkage to an antibiotic resistance gene with the suicide gene in operative linkage with the lambda operator sequence taught by Vasquez et al. because Vasquez et al. taught in the abstract that the use of the suicide gene in the construct allowed the selective expression of a desired gene such as the antibiotic resistance gene of Eliason et al. and Pakula et al. Vasquez et al., at page 12, column 1 recite "[t]he *lac* operator-repressor in one of the best characterized negative control mechanisms in *E. coli*", making the use of the instant claimed operator/repressor obvious. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Eliason et al. with Pakula et al. and Vasquez et al.

19. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eliason et al. with Pakula et al. and Vasquez et al. as applied to claim 1-5, 8-13, 15-28 and 31-34 above, and further in view of WO96/06164.

The claims are drawn to the mutated lambda operator sequence and methods of use as described above, and to a construct where the mutagenesis is performed in a mutator bacterial strain.

WO96/06164 taught (see especially the abstract and the summary of the invention) a mutator bacterial strain used for the well known mutation of a desired sequence of DNA.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant claimed invention to use a mutator strain of bacteria such as the mutator strain of

WO96/06164 because of the well known use of such a strain of bacteria to produce mutations in a selected DNA sequence such as the instant claimed lambda operator sequence.

One of ordinary skill in the art would have been motivated at the time of filing of the instant claimed invention to use a mutator strain of bacteria such as the mutator strain of WO96/06164 because it was well known to those of ordinary skill in the art that a mutator strain of bacteria would produce the desired mutations in a selected sequence of DNA such as the instant claimed lambda operator sequence. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Eliason et al., Pakula et al. and Vasquez et al. with WO96/06164.

Allowable Subject Matter

20. Claim 14 is allowed.

Conclusion

21. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO

DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

September 13, 1999

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER